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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/508,635	05/18/2000	OLIVIER BALLEVRE	P00.0164	7617

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EXAMINER	
LUKTON, DAVID	

ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 02/20/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/508,635	BALLEVRE ET AL.	
	Examiner	Art Unit	
	David Lukton	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 November 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *30,32-35 and 37-41* is/are pending in the application.

4a) Of the above claim(s) *33-35* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *30,32 and 37-41* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Pursuant to the directives of the amendment filed 11/28/03, claims 30, 32, 35, 39-41 have been amended. Claims 30, 32-35 and 37-41 remain pending. Claims 33-35 are withdrawn from consideration.

Applicants' arguments filed 11/28/03 have been considered and found persuasive in part. The previously imposed prior art rejections are withdrawn herewith. However, the §112, first paragraph rejection is maintained.

✧

The following is a quotation of the first paragraph of 35 U.S.C. §112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 30, 32 and 37-41 are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification fails to teach a skilled physiologist how to use protein hydrolyzates and amino acids to promote "recovery" of an organ. As stated in Ex parte Forman (230 USPQ 546, 1986) and In re Wands (8 USPQ2d 1400, Fed. Cir., 1988), the factors to consider in evaluating the need (or absence of need) for "undue experimentation" are the following:

quantity of experimentation necessary, amount of direction or guidance presented, presence or absence of working examples, nature of the invention, state of the prior art, relative skill of those in that art, predictability or unpredictability of the art, and breadth of the claims.

As for the "nature of the invention", it is asserted in the specification (page 8, line 17+) that the disclosed protein hydrolyzates can be used to repair damage to the intestine. Also asserted (page 8, line 20+) is that the disclosed protein hydrolyzates can be used to treat Crohn's disease, diarrhea, colitis or sepsis, and further, that the disclosed protein hydrolyzates can be used to reverse damage to gut epithelial tissue that has resulted from a surgical procedure, or from any other cause. Though not specifically stated, the implication is that various diseases such as hepatitis, cirrhosis of the liver, and kidney infection can be successfully treated. Such diseases cause damage to organ tissue, and if the claimed method is to be effective, the protein hydrolyzates must be effective not only to accelerate wound healing, but overcome the pathological basis of the organ damage. As for the "working examples", the specification discloses results which are consistent with the conclusion that if one administers a mixture of all 20 genetically encoded amino acids to a mammal, the relative weights of the stomach, intestine, duodenum jejunum, liver, gastrocnemius, soleus, and extensor will vary slightly if the ratio of amino acids is altered. This assertion is somewhat suspect, since no statistical analysis has been presented. For example, in the case of the duodenum, the standard deviation would not have to be high at all in order to justify the conclusion that the results are not statistically significant.

Without further information as to the variability in the data (that is presented on page 17), it is not particularly meaningful. The results are also not meaningful, since the amount of lipids and minerals (see page 14) were varied simultaneously with the amino acid composition. Furthermore, the total amount of amino acids varies from from feed mixture to the next. Thus, even if it turns out that the results on page 17 are statistically significant, it has not been determined the extent to which, or even whether, the observed changes in organ weights were the result of varying the amino acid composition, rather than the lipids and minerals. It may be the case that the changes in organ weights were due to changes in the total amount of amino acids administered, rather than variations in the amino acid content. Or maybe the changes in organ weights were due to changes in differential metabolism of the peptide fragments which were produced by the different hydrolysis methods (hydrolyzate 1, hydrolyzate 2 or hydrolyzate 3). Thus, in the disclosed experiments (specification) several different variables have been altered simultaneously, and it is impossible to determine the effects of any one of them taken alone. Furthermore, there is no control experiment. It has not been stated what the results are supposed to be relative to. If the feed compositions (feed 1 - feed 5) were given to rats which were already exhibiting a positive nitrogen balance, would there be any effect at all of the different feeds?

Even if it turns out that the results on page 17 are statistically significant, and if could be determined what the cause (among the numerous variables) of the variance in organ weights might be, the results are still not meaningful with respect to the claimed invention. The

claimed invention is not drawn to a method of randomly altering the weights of selected organs. And even if the claims were drawn e.g., to a method of increasing the weight of the stomach, it is not at all clear how one would proceed. It may be true that if one uses, e.g., feed #5 rather than feed #1, one will obtain a slightly higher weight of the stomach. If it were to turn out that this difference is due to the amino acid content, rather than to the lipids and minerals (or one of the other variables), it would still not be evident how one would translate the results of feed #5 versus feed #1 into a general method of increasing stomach weight. It is not apparent which amino acids are necessary, or which are sufficient; it is not made clear wat degree of hydrolysis will produce the intended results, and which will not. And even if it were true that the specification taught the skilled artisan how to increase the weight of specific organs, there is no teaching as to how that teaching would translate into a showing of enablement for the claimed invention, which is that of using protein hydrolyzates and amino acids to promote "recovery" of an organ.

The results of a second experiment are presented on pages 21-24. What is shown here is that the rate of protein synthesis varies somewhat depending on which of the five feeds is used. The shortcomings of the experimental results described on page 17 apply here as well. First, the results are not statistically significant in the absence of further information as to the variability that is observed from one experiment to the next (for a given feed composition). Second, there are several different variables (with respect to the feed composition itself) which are altered simultaneously. And third, even if there were a clear

assertion as to the specific variable that is supposed to correlate with the increased protein synthesis, and even if there were an experimental basis for such an assertion, this would have little relevance to the claimed invention, which is that of using protein hydrolyzates and amino acids to promote "recovery" of an organ. The specification has presented no evidence that any such correlation exists between rate of protein synthesis, and recovery of an organ from wounding, physical trauma, or damage from an inflammatory condition. The reality is that one cannot "predict" such "recovery" based on rates of protein synthesis.

The following references discusses the issue of statistical analysis, and more importantly the issue of artifacts or invalid conclusions that can be drawn from an inadequate experimental design, or flawed assumption:

Ludbrook (*Clinical and Experimental Pharmacology and Physiology* 28 (5-6) 488-92, 2001)

Bryant (*Pediatric Allergy and Immunology* 9 (3) 108-15, 1998)

Bezeau (*Journal of Clinical and Experimental Neuropsychology* 23 (3) 399-406, 2001)

Bolton (*Journal of Clinical Pharmacology* 38 (5) 408-12, 1998)

Willenheimer (*Progress in Cardiovascular Diseases* 44 (3) 155-67, 2001)

Chung (*Plastic and Reconstructive Surgery* 109 (1) 1-6, 2002)

Atkinson (Chronobiology International 18 (6) 1041-53, 2001).

While several experiments have been conducted, there is no apparent relationship between

the results of those experiments, and the claimed invention. The claimed invention encompasses repair of damage to the intestines, treatment of Crohn's disease, treatment of diarrhea, treatment of colitis or sepsis, treatment of hepatitis, treatment of cirrhosis of the liver, and kidney infection, as well as reversal of damage to gut epithelial tissue. There is no evidence that increasing DNA synthesis or even increasing organ weight engenders a method of promoting wound healing, or of successfully treating a patient whose organs have been damaged by disease, surgery or trauma. "Undue experimentation" would be required to practice the claimed invention.

In response to the foregoing, applicants have argued that the specification teaches how to make the milk protein hydrolyzates. However, this point was never in dispute. Applicants have also argued that the specification teaches how to administer the milk protein hydrolyzates. This is of course true, but virtually any organic materials can be "administered". The fact that something can be administered does not mean that it will exhibit any particular effect.

Next, applicants have argued essentially that if one varies the composition of a milk protein hydrolyzate mixture, one can observe changes in the relative weights of various organs. From this applicants have argued that the experiments demonstrate "recovery" of organs. However, applicants are not correct. As asserted in the specification (page 8, line 17+) that the disclosed protein hydrolyzates can be used to repair damage to the intestine. Also asserted (page 8, line 20+) is that the disclosed protein hydrolyzates can be used to treat

Crohn's disease, diarrhea, colitis or sepsis, and further, that the disclosed protein hydrolyzates can be used to reverse damage to gut epithelial tissue that has resulted from a surgical procedure, or from any other cause. Though not specifically stated, the implication is that various diseases such as hepatitis, cirrhosis of the liver, and kidney infection can be successfully treated. Such diseases cause damage to organ tissue, and if the claimed method is to be effective, the protein hydrolyzates must be effective not only to accelerate wound healing, but overcome the pathological basis of the organ damage. As would be recognized to a skilled physiologist, an observation changes in weights of organs does not in any way amount to a demonstration that Crohn's disease or colitis can be successfully treated. Nor does an observation changes in weights of organs mean that diarrhea can be successfully treated or that sepsis or hepatitis can be successfully treated. Applicants have simply argued that an observation that protein synthesis rate is predictive of efficacy in the treatment of various diseases. However, no evidence has been provided for this, and none is evident.

In accordance with the foregoing "undue experimentation" would be required to practice the claimed invention.

✧

Claims 30, 32 and 37-41 are rejected under 35 U.S.C. 112 second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

- The claims are drawn to a method of promoting "recovery" of an organ. It is unclear as to what the organ is recovering from. The the term could potentially encompass recovery from a wound, physical trauma, or a disease. Despite the amendment, the line between what is encompassed and what is not encompassed remains unclear. For example, one organ is the brain. Is "recovery" from a headache encompassed, or recovery from emotional stress, or recovery from excessive alcohol consumption? It is suggested that the claim be amended to make clear what the mammal is recovering from.

- Each of claims 37-38 is dependent on a cancelled claim.

✧

The following is a quotation of 35 USC §103 which forms the basis for all obviousness rejections set forth in the Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) and (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.
>
> This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made, absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103.

Claims 30 and 37-41 are rejected under 35 U.S.C. §103 as being unpatentable over Nakamura (*J. Dairy Sci.* **78** (6) 1253-1257, 1995) or Masuda (*American Institute of Nutrition* **126**(12) 3063-3068, 1996).

Nakamura discloses that peptides obtained from sour milk exhibit antihypertensive activity. Nakamura does not disclose that antihypertensive agents will promote "recovery" of a damaged heart in hypertensive patients. Masuda provides a similar teaching.

The first point is that the peptides disclosed by Nakamura are milk protein hydrolyzates, since they are formed from milk proteins by the action of proteases. As for the matter of "recovery" of an organ, cardiologists often prescribe antihypertensive agents to patients who meet both of the following conditions: (a) they have suffered damage to the heart muscle, e.g., myocardial infarction or cardiac ischemia, and (b) they are afflicted with hypertension. As it happens, patients who fall into this category are common. In any case, a hypertensive patient who has suffered a "heart attack" would benefit from the antihypertensive peptides of Nakamura. As a consequence of administering these milk protein hydrolyzates, recovery of the cardiac tissue will be promoted.

Thus, the claims are rendered obvious.

✧

Claims 30, 37, 38 are rejected under 35 U.S.C. §103 as being unpatentable over Gordon (USP 5,166,132) or Tomita (USP 5,313,873).

Gordon and Tomita both teach that milk protein hydrolyzates can be used to treat skin. Neither reference uses the phrase "recovery of an organ". However, the skin is an organ of sorts, and if the hydrolyzates are indeed effective to relieve dermatological conditions such as dermatitis, burns and bruises, then this would correspond to "recovery of an organ".

Thus, the claims are rendered obvious.

✧

Claims 30, 37, 38 are rejected under 35 U.S.C. §103 as being unpatentable over Gordon (USP 5,166,132) or Tomita (USP 5,313,873) in view of Verma (USP 6,645,942).

The teachings of Gordon and Tomita are indicated above. Neither reference discloses that skin is an organ. Verma discloses (col 4, line 47) that skin is an organ. Verma does not disclose the use of milk protein hydrolyzates to promote recovery of an organ. Thus a practitioner of the Gordon or Tomita invention would recognize that by administering the milk protein hydrolyzates to a patient, he is promoting recovery of an organ.

✧

Claims 30, 37, 38 are rejected under 35 U.S.C. §103 as being unpatentable over Smith (WO 97/16460).

Smith discloses that a casein hydrolyzate has growth promoting activity. Smith does not explicitly state that the casein hydrolyzate will promote "recovery of an organ". However, one of ordinary skill would expect that growth of organs will be promoted, those of infants, as well as those of adults who have suffered damage to an organ as a result of disease, injury or surgical procedure. The examiner does not argue that only tissues that are present in organs will grow, while those tissues present outside of organs will be unaffected. But the claims do not preclude the possibility that the recovery of non-organ

tissue will be promoted in addition to the recovery of organs.

Thus, the artisan of ordinary skill would have expected that recovery of tissues both inside and outside of organs will be promoted.

✧

Claims 30, 32, 37-41 are rejected under 35 U.S.C. §103 as being unpatentable over Jolles (USP 4,716,151).

Jolles discloses that tripeptides obtained from hydrolysis of milk proteins will stimulate the immune system. Jolles does not disclose that the recited tripeptides will promote recovery of an organ in an immune compromised patient.

As applicants are likely aware, the most common cause of death in immune compromised patients is opportunistic infections. For example, candida albicans and/or pneumococcus often infects the lungs of AIDS patients. Bacterial infections of the kidney are also common; infections can also occur in the gut. Such infections (bacterial, viral or fungal) flourish because the immune system cannot suppress them. As a consequence of administering a tripeptide according to Jolles (or a mixture of two or more such tripeptides), the immune system will be able to combat the infections, leading to "recovery" of the erstwhile infected organs. Applicants may be inclined to argue that the claims do not require immune stimulation, or that the mechanism of action of their hydrolyzates is different from the hydrolyzates of Jolles. However, what matters from the patentability standpoint is the end result. The claims require that recovery of an organ occur; the medical

specialist (of ordinary skill) would have expected that such recovery will occur in an immune compromised patient. It is noted also that claim 30 recites that the hydrolyzate be effective to increase protein content or synthesis. However, the physiologist of ordinary skill would have expected that if the peptides were administered to a mammal (e.g., human or rat) exhibiting negative nitrogen balance (i.e., insufficient protein), protein synthesis (relative to protein breakdown) will be greater than would have been the case had the state of negative nitrogen balance been allowed to continue. Thus, suppose that a physiologist had two rats of the same species, weight and gender. The "first" rat is placed on "starvation" diet which is insufficient to support positive nitrogen balance. The first rat is then administered one or more of the tripeptides of Jolles in an amount sufficient to produce a positive nitrogen balance. The expected result will be that protein synthesis in various organs and tissues will be increased. Accordingly, increase in protein synthesis becomes a demonstrated inherent property of the tripeptides. If one of the tripeptides is then administered to the "second" rat which has been both immunosuppressed and infected (e.g., candida, pneumococcus, infection of the kidney), the result will be, at least according to Jolles, elimination of the immunosuppressed state. It would then follow that the infection will be eradicated. At the same time, the administered tripeptide has the property of increasing protein synthesis, even if that is not the mechanism by which it promotes recovery of the organ. The claims do not require that a therapeutic effect occur directly as a result of an increase in protein synthesis, and the claims do not preclude a protein

hydrolyzate from having a specific pharmacological effect in addition to its property of increasing protein synthesis.

Thus, the claims are rendered obvious.

✧

Claims 30, 32, 37-40 are rejected under 35 U.S.C. §103 as being unpatentable over Vickery (USP 6,203,820).

Vickery discloses (col 3, lines 17-18) that arginine regenerates the liver. Also disclosed (col 3, line 44) is that isoleucine promotes wound healing and muscle growth. Also disclosed (col 4, lines 57-62) is that a mixture of amino acids can be prepared by enzymatic hydrolysis of milk proteins.

Vickery does not explicitly state that milk protein hydrolyzates will promote recovery of the liver, or that milk protein hydrolyzates will promote recovery of a wounded organ (e.g., by injury, disease or surgical procedure). However, if the various assertions are to be taken at face value, the biochemist of ordinary skill would have concluded that by combining the proteolytic enzyme with the milk proteins, amino acids such as arginine and isoleucine will be released, and that those amino acids will be effective to promote recovery of the liver, and to promote recovery of a wounded organ.

Thus, the claims are rendered obvious.

✳

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Lukton whose telephone number is 571-272-0952. The examiner can normally be reached Monday-Friday from 9:30 to 6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low, can be reached at 571-272-0951. The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

DAVID LUKTON
PATENT EXAMINER
GROUP 1600